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Complications of Transvenous Right Ventricular Endomyocardial Biopsy in Adult Patients With Cardiomyopathy: A Seven-Year Survey of 546 Consecutive Diagnostic Procedures in a Tertiary Referral Center

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To determine the incidence, nature and subsequent management of complications occurring during right ventricular endomyocardial biopsy in patients with cardiomyopathy, all events occurring during 546 procedures in 464 consecutive patients were prospectively recorded. The internal jugular vein was the primary site of introduction in 96% of cases. A total of 33 complications (6%) occurred: 15 (2.7%) during catheter insertion including 12 arterial punctures (2%), 2 vasovagal reactions (0.4%) and 1 episode of prolonged bleeding (0.2%), all without sequelae; 18 (3.3%) during biopsy included 6 arrhythmias (1.1%), 5 conduction abnormalities (1%), 4 possible perforations (0.7%) and 3 definite perforations (0.5%) (pericardial fluid). Two (0.4%) of the three patients with a perforation died.

There was no secular trend in the complication rate, nor were complications associated with specific clinical or hemodynamic characteristics. It is concluded that the overall rate of endomyocardial biopsy complications (6%) is low, but mortality may occur.

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The pathophysiology, natural history and appropriate treatment of primary myocardial disease remain poorly understood. Routine cardiac catheterization techniques, although able to determine the severity of myocardial failure and assess the short-term response to therapy, have failed to significantly increase our knowledge of the etiology and pathophysiology of cardiomyopathy. The advantage of obtaining heart muscle from patients with primary myocardial failure has long been acknowledged (1). The histologic and biochemical analysis of heart tissue obtained by endomyocardial biopsy is the most likely technique to advance our understanding of these disorders (2,3). Currently, the direct clinical benefits of endomyocardial biopsy are limited to specific groups of patients with primary or secondary cardiac disease (1).

Proper selection of patients considered candidates for endomyocardial biopsy is enhanced by better insight into the balance between risks and benefits associated with this invasive procedure. Because endomyocardial biopsy is performed on a regular basis in only a limited number of centers, little information is available on the rate of complications experienced during diagnostic biopsy procedures in cardiomyopathy patients. To that purpose, the current report reviews all diagnostic right ventricular endomyocardial biopsies performed in a tertiary referral center.

Methods

Source of patients. Diagnostic right ventricular endomyocardial biopsy became available on a routine basis in our center in 1982; since then, the hospital has served as a referral center for other institutions in the Baltimore region with an estimated total population of 2 to 3 million people. Most diagnostic biopsies were performed in subjects who presented with recent (<6 months' duration) onset of symptoms of heart failure and in whom other plausible causes of left ventricular dysfunction such as coronary artery disease and significant valvular heart disease had been excluded by other diagnostic procedures. Biopsy was also performed in patients in whom, on the basis of available clinical evidence, a secondary cardiomyopathy was considered likely, for instance in patients suspected of amyloidosis or in those previously treated with doxorubicin.

Biopsy technique. The right internal jugular vein was the preferential site of introduction for the procedure. A modified Caves-Schultz bioptome (4) or a disposable system (5) was used. All but 10 biopsies were performed by the same physician (K.L.B.). The biopsy method employed has been described extensively elsewhere (6). In short, procedures were performed in a postabsorptive state without premedication. The internal jugular vein was identified before prepa-

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ration of the site with betadine and alcohol. The skin and immediate subcutaneous tissue of the site were anesthetized with lidocaine with use of a small needle. A larger needle was used to anesthetize the area of the internal jugular vein and to confirm the position of the vein. Canulation of the internal jugular vein was attempted in the middle third of the neck. An 18-gauge Amplatz needle was inserted in the direction of the venous source. The Teflon portion of the Amplatz apparatus remained in the vein and a 0.038-in. (0.097-cm) guide wire was inserted through it into the superior vena cava. A self-sealing, size 9 sheath and dilator were then inserted over the wire. The sheath was flushed with heparinized saline solution and the 50-cm Caves-Schultz bioptome inserted through the sheath with the tip pointed toward the lateral atrial border. The bioptome was rotated anteriorly about 180° in the mid atrium before being advanced through the tricuspid valve. The bioptome was then slowly advanced toward the right ventricular septum. Once contact with the septum was confirmed by premature complexes, the bioptome was withdrawn 1 to 2 cm, its jaws opened and slowly advanced to engage the septum. Gentle forward pressure was maintained while the jaws were closed. The bioptome containing the specimen was removed by gentle traction on the shaft.

In the great majority of patients, right heart filling pressures and cardiac output were measured with a Swan-Ganz catheter after completion of the biopsy. The femoral venous approach was used in the minority of cases utilizing a disposable bioptome and a preformed sheath. The sheath in this system is positioned in the right ventricle.

Complications. Beginning in 1982, all adverse events related to the procedure were required to be recorded on a worksheet immediately after the biopsy. For the purpose of this study, the following complications associated with the introduction of the catheter were considered: arterial puncture, with or without the development of hematoma, prolonged bleeding at the site of introduction, pneumothorax, infection and vasovagal reaction. Complications related to the manipulation of the bioptome in the heart, such as catheter-induced rhythm disturbances, atrioventricular (AV) block or bundle branch block, were also assessed. The most serious incidents encompassed those associated with the actual acquiring of cardiac tissue, such as suspected or definite myocardial perforation. These included pain during the biopsy, the sudden development of bradycardia accompanied by hemodynamic instability (a decrease in systolic blood pressure of >30 mm Hg requiring fluid replacement) and clinical, hemodynamic or echocardiographic evidence of sudden accumulation of pericardial fluid. Clinical characteristics and hemodynamic variables between patients with and without complications were compared with Student's *t* test.

Results

During the 7-year study period, a total of 546 diagnostic biopsies were performed in 464 patients without cardiac transplantation. During the last 4 years, the number of procedures performed has gradually increased to approximately 100/year. Myocardial tissue adequate for diagnosis was obtained during all procedures.

Table 1. Clinical Characteristics of 464 Patients

Number of procedures	546
Male	278 (60%)
Age (yr)	43 ± 14
No. of biopsy specimens/procedure	6 ± 2
RA mean (mm Hg)	7 ± 5
PCW mean (mm Hg)	16 ± 10
CI (liters/min per m²)	2.4 ± 0.6

Data are presented as mean values ± SD. CI = cardiac index; PCW = pulmonary artery wedge pressure; RA = right atrial pressure.

Patient characteristics (Table 1). Many patients had severe heart failure at the time of the procedure: the mean right atrial pressure was >10 mm Hg and the capillary wedge pressure >24 mm Hg in 25% of the 392 patients in whom these measurements were recorded. The internal jugular vein was the primary site of introduction in 525 (96%) procedures; the subclavian approach was preferentially used in 3 procedures (0.5%) and the femoral approach in 7 (1.3%). Failure to obtain entry in the internal jugular vein necessitated an alternative route in only 11 procedures (2%).

Complications (Table 2). A total of 33 complications (6%) occurred during the 546 biopsy procedures. The most frequent complication, arterial puncture (n = 12), caused no sequelae in any subject. A mild vasovagal reaction not requiring hydration occurred in two patients. One patient

Table 2. Complications of Endomyocardial Biopsy in 546 Procedures

	No.		%
During introduction	15		2.7
Arterial puncture	12		2.2
Prolonged bleeding	1		0.2
Vasovagal reaction	2		0.4
Pneumothorax	0		0
Neurologic events	0		0
During biopsy	18		3.3
Arrhythmias	6		1.1
Supraventricular tachycardia		5	0.9
Ventricular tachycardia		1	0.2
Conduction abnormalities	5		1
Bradycardia	1		0.2
Right bundle branch block	1		0.2
Complete heart block	1		0.2
Complete heart block (preexisting LBBB)	2		0.4
Perforation, possible	4		0.7
Pain with biopsy	3		0.5
Blood pressure decrease	1		0.2
Perforation, definite	3		0.5
Pericardial fluid	1		0.2
Death	2		0.4

LBBB = left bundle branch block.

who had been taking salicylates had prolonged venous oozing but did not require transfusion. Hoarseness or Horner's syndrome, suggestive of traumatic dysfunction of the vagus branch, and pneumothorax were not experienced.

Arrhythmias. Supraventricular tachycardia was the most frequently observed arrhythmia. Medical therapy for paroxysmal atrial tachycardia was necessary on four occasions; this arrhythmia spontaneously converted to sinus rhythm in one other case. Long runs of 8 to 10 ventricular complexes caused by entry of the bioptome in the right ventricle in one patient disappeared spontaneously. Conduction abnormalities occurred in five patients. Sudden bradycardia accompanied by a 30-mm Hg decrease in blood pressure, most likely the result of a high septal biopsy (n = 1), resolved without therapy within 3 min. Heart block or bundle branch block (n = 4) was transient and without significant hemodynamic consequences in all instances; no temporary pacemaker has been employed because of such a complication. In two of the three cases of complete heart block, patients had a preexistent left bundle branch block.

Heart perforation. Clinical evidence of heart perforation was obtained in three subjects, providing a rate of definite perforation of 0.5%. In one subject, perforation, suspected because of the sudden appearance of typical visceral pain immediately after the acquirement of cardiac tissue, was confirmed by right heart catheterization demonstrating equalization of filling pressures and low cardiac output and by echocardiographic demonstration of a moderate pericardial effusion. The effusion increased during the next 2 h but stabilized thereafter. The patient's condition remained stable during this period and no intervention was necessary. The effusion subsequently resolved over several days.

Perforation proved to be lethal in two subjects. The first death occurred in a 72-year old man who had profound congestive heart failure with massive ascites and was stuporous at the time of study. Although the biopsy procedure (utilizing the internal jugular vein approach with the Stanford Caves bioptome) appeared to proceed without difficulty, the patient was found to be without respiration immediately after the last biopsy specimen was taken. Electrocardiographically, sinus rhythm had been present continuously during the procedure. The patient proved to be without a peripheral pulse and electromechanical dissociation was diagnosed. Echocardiography established the presence of a large pericardial effusion. Unfortunately, pericardiocentesis did not improve the patient's cardiovascular state; his condition deteriorated rapidly and he died after unsuccessful cardiac life-support resuscitation.

The second subject who died as a result of heart perforation was a 71-year old woman with a short history of cardiac failure and atrial fibrillation. The biopsy procedure was performed from the right femoral vein, because access through the internal jugular or subclavian vein was inadequate to accept the bioptome. A disposable bioptome was inserted through the right ventricular sheath and serial biopsy specimens were taken from several sites in the right ventricle. The bioptome advanced excessively during the last passage because of repositioning of the sheath. Immediately, symptoms of chest pain and bradycardia developed and the systolic blood pressure decreased to approximately 70 mm Hg. An echocardiogram revealed the presence of a large pericardial effusion with right ventricular collapse compatible with tamponade. Despite various measures to improve the subject's circulation, including inotropic support and pericardiocentesis, the patient's condition deteriorated rapidly and she died in cardiogenic shock. In three additional instances patients reported chest pain during biopsy and in one a decrease in blood pressure required 500 ml of fluid replacement. These four patients had no further sequelae.

Table 3. Trends in Numbers and Type of Complications of Endomyocardial Biopsy

Year	Number of Biopsies	Complications					
		Total		Introduction		All Other	
		No.	%	No.	%	No.	%
1983	28	—	—	—	—	—	—
1984	51	4	8	2	4	2	4
1985	55	3	6	1	2	2	4
1986	98	6	6	4	4	2	2
1987	89	6	7	3	3	3	3
1988	113	7	6	3	3	4	3
1989	134	7	6	2	2	5	4
Total	546	33	6	15	2.7	18	3.3

Although the two fatal incidents occurred in elderly subjects no difference was found to be present in clinical variables such as age, gender, blood pressure level or hemodynamic variables between subjects with and without complications during biopsy. This was also the case when this analysis was repeated after the exclusion of those complications that were related to the introduction of the bioptome (i.e. arterial puncture, bleeding and vasovagal reaction).

Secular trend in complications (Table 3). The presence of a single operator allowed evaluation of a secular trend in complications. No relation was found to be present between complications and the year of biopsy (a single procedure performed in 1982 was added to the number of 27 biopsies in 1983), nor did the rate of complications significantly decrease with time. The rate of complications associated with the procedure varied between 6% and 8% in all years; the rate of more serious events varied between 2% and 4%.

Discussion

These data document in detail the risks of endomyocardial biopsy at a single medical institution. Although larger series have been reported, this analysis is unique in several respects: 1) all complications were reported including those related to introduction of the venous sheath and perfor-

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mance of the endomyocardial biopsy; 2) complications were studied in a prospective manner and recorded immediately after biopsy; 3) the technique utilized was almost exclusively of one type; and 4) the study group represents the largest series of patients with cardiomyopathy studied at a single institution. Other multicenter, multitechnique retrospective reports obtained by questionnaire from patients with cardiomyopathy or those undergoing cardiac transplantation cannot be considered equivalent.

Cardiac perforation and pericardial tamponade. Although complications occur relatively infrequently and the procedure can be considered safe, serious consequences can occur including death. As reported, there were two deaths in our series (mortality rate 0.37%). Several important lessons have been learned from these events that may be of benefit to other physicians performing heart biopsies. First, electromechanical dissociation occurring during performance of an endomyocardial biopsy should be considered diagnostic of right ventricular perforation with pericardial tamponade or pneumothorax. Therefore, in all patients, but particularly those incapable of reporting discomfort, continuous blood pressure monitoring should be performed. Second, tamponade may not be relieved by pericardiocentesis. Acute pericardial bleeding may result in formation of pericardial clots that prevent effective aspiration and drainage of the pericardial sac, especially with persistent transmyocardial bleeding. Pericardial exploration is strongly recommended in patients who do not respond promptly to pericardiocentesis. Finally, disposable systems utilizing sheaths that remain in the ventricle may predispose to perforation unless the sheath is clearly free in the ventricular cavity without engaging the right ventricular free wall.

Comparison with previous reports. The overall complication rate of endomyocardial biopsy in other large series includes a reported risk of <1% in the Stanford series of approximately 4,000 biopsies (7) and 1.55% in the European experience of 3,097 biopsies (7). Two worldwide surveys have reported complication rates of 1.17% in 6,739 procedures (8) and 1.67% in 2,337 (9). We report an overall complication rate of 6% in 546 procedures. Other more detailed single center reports are more compatible with our results. The Mayo clinic (10) reported a complication rate of 4.4% in 100 consecutive diagnostic biopsy procedures. Hosenpud (11) reported a 14% complication rate in Oregon's first 50 procedures. Anderson and Marshall (12) reported a 11% complication rate in adults and Yoshizato et al. (13) a 12% complication rate in pediatric patients. None of these previous series were as inclusive as ours in evaluating the entirety of risks associated with endomyocardial biopsy. Nonetheless, it is this complete detailing of complications, major and minor, that must be presented to patients and colleagues in addressing the advisability of undergoing this procedure.

Complications of venous catheterization. These are infrequently reported in other series. We experienced no pneumothorax or neurologic sequelae, 12 carotid artery punctures (without sequelae), 2 vasovagal reactions not requiring atropine or fluid administration and 1 prolonged venous oozing in a patient on long-term aspirin therapy. Pneumothorax has occurred in 3 of 4,000 patients at Stanford (7), 10 of 6,739 (8) and 3 of 2,337 patients (9) in two worldwide surveys, 1 of 100 at the Mayo Clinic (10) and in 1 of 53 pediatric patients (13). Low et al. (5) are the only group to report the frequency of carotid artery puncture while obtaining venous access, in 11 of 600 patients, which was similar to our rate. Failure to gain entry in the venous cannulation site occurred in 10% of Hosenpud's patients (11), 12% of the patients of Anderson and Marshall (12) and 3% of pediatric patients (13). Venous hematoma or significant local pain was reported exclusively by Anderson and Marshall (12) with a frequency of 16%. Nippoldt et al. (10) were the only other investigators to report a vasovagal reaction rate, which they found to be 1%. Pneumothorax may be avoided by approaching the internal jugular vein one third of the way from the clavicle to the jaw and angling the needle more perpendicularly to the vein, thereby preventing puncture of the lung apex. Failure to gain jugular venous access is usually due to low volume, indistinct landmarks or tamponade of the venous sheath by excessive local anesthesic agent or bleeding. Vasovagal response could probably be eliminated by the use of atropine. We do not use premedications (particularly atropine) so that filling pressures and heart rate are unaffected for subsequent right heart catheterization assessment of left ventricular compromise.

Arrhythmias. Complications during the biopsy procedure include arrhythmia, conduction abnormalities and perforation. We observed five supraventricular arrhythmias, all in patients with a prior history of paroxysmal atrial tachycardia or fibrillation. The Stanford group (7) report only three episodes of atrial fibrillation in 4,000 biopsies (one of these episodes occurred in their initial 19 patients). Nonsustained ventricular tachycardia occurred in one of our patients, who had a prior history of this arrhythmia. Other centers report ventricular tachycardia as a complication of biopsy in 1 of 4,000 at Stanford (7), 3 of 100 at the Mayo Clinic (10), and 4 of 53 in pediatric patients (13). Therefore, those patients with a history of arrhythmia are at increased risk for arrhythmic complications at the time of biopsy. Whether or not patients have a history of arrhythmia, appropriate precautions for arrhythmia management must be taken because of the propensity of endocardial stimulation to induce potentially lethal arrhythmias. Additionally, as the right ventricular biopsy produces pressure against the right ventricular septum, right bundle branch block may be created or complete heart block result in patients with preexisting left bundle branch block. We observed four such events. In the survey of 6,739 biopsies reported by Sekiguchi and Take (8), 11 instances of bundle branch block and 2 of AV block occurred. Only Ali et al. (14) reported a significant incidence of bundle branch block in 3 of 28 patients.

Cardiac perforation. Right ventricular free wall perforation with pain, pericardial effusion, tamponade and death

remains the most significant and dangerous complication of endomyocardial biopsy. We report four possible perforations and three definite myocardial perforations (definite 0.5%), two of which were fatal. We believe that all patients experiencing sharp pain during endomyocardial biopsy have had myocardial perforation with pericardial irritation. Other investigators (15) have reported a chest pain incidence of nearly 10% with biopsy despite a definite perforation rate of only 1.2% (5 of 413 procedures). In contrast, Sekiguchi and Take (8) reported only four occurrences of chest pain in 6,739 procedures. Anderson and Marshall (12) reported events compatible with possible perforation in 3 of 69 patients. Definite perforation with tamponade was reported by Mason (16) (4 of 1,300). Sekiguchi and Take (8) (28 of 6,739) and Richardson (9) (15 of 2,337). In the latter series six patients required surgical exploration. The risk of perforation is increased in the cardiomyopathy group as opposed to the transplant group because of the lack of epicardial scar formation in the former. Additionally, although the risk is increased by factors that enlarge the right ventricular cavity, increase pulmonary artery pressure or alter hemostasis, we identified no clinical variables such as age, gender and vital signs or hemodynamic variables to serve as markers of risk. Although we continue to believe that right ventricular perforation should not occur, there is no evidence that the frequency of this complication is decreased as a result of experience with the procedure. Early diagnosis of this complication, effective drainage or exploration should prevent mortality.

Conclusions. Although endomyocardial biopsy does have associated risks, only perforation is of major significance. Most procedures can be performed with little or no discomfort on an outpatient basis. The benefits of analysis of endomyocardial biopsy tissue are likely to increase as histologic analysis is replaced by more detailed functional and biochemical studies of myopathic tissue. Only by completely reporting the institutional, prospectively determined risks of the procedure can the potential benefits be assessed.

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